Excessive daytime sleepiness in idiopathic restless legs syndrome: characteristics and evolution under dopaminergic treatment

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Abstract: BACKGROUND/AIMS: Whereas insomnia is frequent in restless legs syndrome (RLS), little is known about daytime sleepiness. We studied a series of 27 consecutive patients with idiopathic RLS in order to identify the characteristics and evolution of excessive daytime sleepiness (EDS) under dopaminergic treatment. METHODS: Patients were assessed by clinical examination, questionnaires and video-polysomnography (PSG). Sleepy patients, as defined by Epworth Sleepiness Scale (ESS) >10, were also assessed by the multiple sleep latency test (MSLT). We excluded RLS patients with other sleep-wake disorders, in particular chronic sleep deprivation. RESULTS: Mean age was 56 years, the mean International RLS Study Group Rating Scale score was 24 at baseline. Ten (37%) of the 27 patients reported EDS. RLS patients with sleepiness had a higher amount of total sleep time ($p = 0.029$) on PSG and a mean sleep latency of 6.4 min on MSLT. No other differences regarding clinical or polysomnographic parameters were found. RLS severity improved in all patients under dopaminergic treatment ($p = 0.001$); this was also the case for the ESS score in sleepy patients ($p = 0.007$). CONCLUSION: In our series of RLS patients, EDS was common, characterized by longer sleep (PSG) and reduced sleep latencies on MSLT. Under dopaminergic treatment, both RLS severity and ESS improved.

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Excessive Daytime Sleepiness in Idiopathic Restless Legs Syndrome: Characteristics and Evolution under Dopaminergic Treatment

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Key Words
Dopaminergic treatment · Excessive daytime sleepiness · Hypersomnia · Polysomnography · Restless legs syndrome

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Introduction

The restless legs syndrome (RLS) is a common neurological sleep disorder affecting 0.5–10% of the general population [1–3], which is twice as common in women than in men [4, 5]. The International RLS Study Group defined four minimal diagnostic criteria [5–7], and supportive criteria include (1) a positive family history of RLS, (2) a positive response to dopaminergic therapy and (3) periodic limb movements (PLM) during wakefulness or sleep (PLMS). PLMS occur in about 80% of RLS patients [8]. RLS is a heterogeneous disorder and can be idiopathic, familiar or symptomatic mainly in association with iron deficiency, pregnancy, anemia or uremia [9–11]. RLS symptoms and PLMS often disrupt the night sleep and impair sleep quality. Whereas insomnia is a frequent complaint in RLS [3, 8, 12], there is little knowledge about

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determinants of excessive daytime sleepiness (EDS) as well as its evolution under dopaminergic treatment [12]. In five previous studies, a subpopulation of RLS patients with daytime sleepiness [Epworth Sleepiness Scale (ESS) >10] has been identified [3, 13–16]. Two studies looked at the association of dopaminergic treatment and sleepiness in RLS patients [17, 18]. The aim of this study was to assess characteristics of RLS with EDS and to evaluate the evolution of EDS under dopaminergic treatment.

Patients and Methods

Ethical Aspects

The study has been reviewed and approved by the Institutional Review Boards.

Clinical Assessment

The data of 27 consecutive patients (13 men) with untreated idiopathic RLS were retrospectively analyzed. Additional sleep-wake disorders (e.g. narcolepsy and sleep-disordered breathing), chronic sleep deprivation, in particular behaviorally induced insufficient sleep syndrome, and major systemic, neurological and psychiatric disorders were excluded by medical history, clinical examination, questionnaires (e.g. International RLS Study Group Rating Scale (IRLS) and ESS), video-polysomnography (PSG) and blood tests (including iron, renal and thyroid parameters). All patients were free of any CNS medication. EDS was defined as ESS >10 [19], and severe EDS as ESS >14.

Nocturnal Sleep Studies

A conventional PSG including four-channel EEG and left and right anterior tibialis electromyography were performed in all patients (Medcare Somnologica Studio software, version 3.2). Sleep stages [20] and arousals were scored manually, and apneas/hypopneas and PLM were reanalyzed automatically and checked visually, all according to international criteria. Sleep onset was defined as the first epoch of rapid eye movement or non-rapid eye movement 2–4 sleep. RLS patients with EDS (n = 10) were also assessed by the multiple sleep latency test (MSLT) [21] after the PSG night.

Treatment

All patients received dopaminergic treatment, e.g. pramipexole (n = 12, mean dose 0.56 mg/day), ropinirole (n = 8, 0.63 mg/day) and others (cabergoline; n = 4, 1.25 mg/day, and pergolide; n = 3, 0.67 mg/day) after the initial assessment and were assessed clinically again including sleep questionnaires (IRLS and ESS) 2 months later. In 3 of the 10 sleepy patients, MSLT was repeated under treatment.

Data Analysis

Statistical analysis was performed using SPSS® software (version 13). Due to the small data set, we used non-parametric tests (e.g. the Mann-Whitney test) to compare the independent groups of sampled data. Significance was defined as $p < 0.05$.

Results

Clinical Features

The main demographic characteristics, ESS, IRLS, PSG and MSLT data are presented in table 1. The mean IRLS score was 24.2 at baseline and improved to a mean of 16.9 ($p < 0.001$) under dopaminergic treatment. Females had a higher IRLS score (26.6 vs. 21.7 in men, $p = 0.031$) at baseline. EDS was found in 10 (37%) and was severe in 6 (22%) of the 27 patients.

Sleep Studies

Sleepy RLS patients had a higher amount of total sleep time (TST) on PSG (378 vs. 313 min; $p = 0.029$; table 1). During treatment, mean sleep latency increased in all 3 patients by a mean of 1.8 min (±1.2).

Dopaminergic Treatment

At the 2-month follow-up, ESS was significantly lower only in sleepy RLS patients ($p = 0.007$). In 4 of our patients, ESS increased under treatment (pramipexole, n = 2, and ropinirole, n = 2). Three of them were in the group of the non-sleepy RLS patients (mean ESS: 7.3 at baseline and 9.7 under treatment). One patient was within the sleepy group (mean ESS: 11 at baseline and 13 during treatment). No sleep attacks occurred.

Discussion

Our results are in line with previous findings [12–16] indicating the existence of a substantial subgroup of RLS patients with EDS. Sleepy RLS patients also exhibited other features of hypersomnia, e.g. longer TST on PSG.

The existence of EDS and hypersomniac features in our series of RLS patients cannot be explained by coexisting sleep disorders, differences in demographics, clinical features, overnight sleep, PLMS, arousal index or medication. Insufficient sleep (e.g. the behaviorally induced insufficient sleep syndrome), one of the most common causes of EDS, was excluded by medical history and sleep questionnaires.

No significant differences were found between sleepy and non-sleepy patients. In contrast to the literature [14, 15], in our patients no association between the frequency of RLS symptoms and EDS or insomnia and EDS was found.

The origin of EDS in RLS remains unknown. Dopamine plays an important role in the modulation of sleep and wakefulness [22]. Insufficient dopamine transmis-

Table 1. Main demographic characteristics, ESS, IRLS, MSLT and PSG results at baseline and follow-up (ESS and IRLS)

	All patients (n = 27)	Non-sleepy (n = 17)	Sleepy (n = 10)	p value sleepy vs. non-sleepy
Age	56.4 ± 11	56.4 ± 13	56.4 ± 7	NS
Body mass index	25.1 ± 3.4	25.5 ± 3.4	24.4 ± 3.5	NS
IRLS	24.2 ± 5.6	24.7 ± 4.8	23.3 ± 7	NS
ESS	9.9 ± 4.1	7.1 ± 2.2	14.5 ± 1.5	<0.001
IRLS at follow-up	16.9 ± 7.1	17.1 ± 8	16.6 ± 5	NS
ESS at follow-up	7.5 ± 4	5.9 ± 4	10.2 ± 3	0.004
PSG				
Sleep latency N2, min	36.9 ± 55	50.7 ± 65	13.4 ± 12	NS
Sleep latency REM, min	106.6 ± 60.2	97.7 ± 61	122 ± 59	NS
Total sleep time, min	336.7 ± 75	313 ± 82	378 ± 38	0.03
PLMS index (TST)	26.6 ± 17.9	27.1 ± 21	25.6 ± 11	NS
Arousal index (TIB)	12.9 ± 10.5	11.9 ± 9	14.5 ± 13	NS
Sleep efficiency, % of TIB	83 ± 12.1	83.3 ± 10	82.4 ± 15	NS
NREM1 sleep, % of TST	10.2 ± 6.2	10.8 ± 8	9.1 ± 3	NS
NREM2 sleep, % of TST	48.1 ± 10.4	47.5 ± 9	49.1 ± 13	NS
Slow-wave sleep, % of TST	12.3 ± 8.7	13.6 ± 10	9.9 ± 7	NS
REM sleep, % of TST	12.2 ± 5.9	11.1 ± 7	14 ± 4	NS
Wake, % of TIB	16.9 ± 11.6	16.2 ± 10	18.2 ± 15	NS
MSLT (n = 10)				
MSL, min	–	–	6.4 ± 2.7	–
Patients with MSL <5 min, n	–	–	3	–
Patients with SOREM, n	–	–	1	–

Means ± SD. REM = Rapid eye movement; TIB = time in bed; NREM1/2 = non-REM sleep stage 1/2; SOREM = sleep-onset REM period(s).

sion has been implicated in the pathophysiology of RLS [23] and has been suggested to be involved in EDS of other sleep disorders. Neurochemical studies in the cerebrospinal fluid suggested that patients with idiopathic hypersomnia might have an altered monoaminergic system as possible sign of a dopaminergic dysfunction [24]. In addition, dopamine antagonists usually exacerbate RLS symptoms and EDS. The possibility of an insufficient dopaminergic transmission is supported by the observation that all evaluated agents that enhance dopamine activity reduce RLS symptoms [10].

Indeed, also in our study, dopaminergic treatment was efficient for RLS symptoms (assessed by IRLS), but also for EDS in sleepy patients (assessed by ESS and mean sleep latency). This finding is in contrast to Parkinson's disease, where dopamine therapy often leads to sleepiness. Nevertheless, also in our study there were 4 patients, mainly from the non-sleepy group, where sleepiness increased under dopaminergic treatment. No sleep attacks occurred [18, 25]. These observations point to the necessity to take EDS into consideration in non-treated and treated RLS patients.

A retrospective study bears potential bias when assessing the treatment effect, which is in our case dopaminergic treatment.

In conclusion, in our series of RLS patients, EDS was common (occasionally severe) and could be objectively confirmed by MSLT. Dopaminergic treatment improved RLS symptoms and EDS. We suggest the existence of a subgroup of sleepy and even 'hypersomniac' RLS patients in whom EDS is possibly due to a dopaminergic dysfunction different from the pathogenetic mechanism of RLS in non-sleepy patients.

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